

Supplementary information— G Eagle, J Zhuang, et al.

**Supplementary Table S1. Proteins found to be significantly differentially expressed ( $P < 0.05$ ) between UM-CLL and M-CLL in previous proteomic studies**

Accession	Protein	Expression (UM/M)	Sample number		Method	Reference
			UM-CLL	M-CLL		
P31946	14-3-3 protein beta	↓	6	6	2D-GE + MALDI-ToF-MS	Cochran et al (2003)
P39687	Acidic leucine-rich nuclear phosphoprotein 32 family member A	↑	1	1	ICAT + LC-MS/MS	Barnidge et al (2005)
Q9UKV3	Apoptotic chromatin condensation inducer in the nucleus	↓	6	22	iTRAQ + MALDI MS/MS	Alsagaby et al (2014)
P10644	cAMP-dependent protein kinase type I-alpha regulatory subunit	↑	3	3	2D-DIGE + MALDI-ToF-MS + LC-MS/MS	Perrot et al (2011)
P10606	Cytochrome c oxidase subunit 5B, mitochondrial	↓	1	1	ICAT + LC-MS/MS	Barnidge et al (2005)
P14854	Cytochrome c oxidase subunit 6B1	↓	1	1	ICAT + LC-MS/MS	Barnidge et al (2005)
P19388	DNA-directed RNA polymerases I, II, and III subunit RPABC1	↑	3	3	2D-DIGE + MALDI-ToF-MS + LC-MS/MS	Perrot et al (2011)
P47757	F-actin-capping protein subunit beta	↓	6	6	2D-GE + MALDI-ToF-MS	Cochran et al (2003)
P07203	Glutathione peroxidase 1	↑	1	1	ICAT + LC-MS/MS	Barnidge et al (2005)
P14317	Hematopoietic lineage cell-specific protein	↑	3	3	2D-DIGE + MALDI-ToF-MS + LC-MS/MS	Perrot et al (2011)
P14317	Hematopoietic lineage cell-specific protein	↓	3	3	2D-DIGE + MALDI-ToF-MS + LC-MS/MS	Perrot et al (2011)
P68871	Hemoglobin subunit beta	↓	1	1	ICAT + LC-MS/MS	Barnidge et al (2005)
P02042	Hemoglobin subunit delta	↓	1	1	ICAT + LC-MS/MS	Barnidge et al (2005)
P22626	Heterogeneous nuclear ribonucleoproteins A2/B1	↑	1	1	ICAT + LC-MS/MS	Barnidge et al (2005)
P30484	HLA class I histocompatibility antigen, B-46 alpha chain	↓	1	1	ICAT + LC-MS/MS	Barnidge et al (2005)
P08865	Laminin-binding protein precursor	↓	6	6	2D-GE + MALDI-ToF-MS	Cochran et al (2003)
Q14847	LIM and SH3 domain protein 1	↑	6	22	iTRAQ + MALDI MS/MS	Alsagaby et al (2014)

	P06748	Nucleophosmin	↑	4	4	2D-GE + LC-MS/MS	Rees-Unwin et al (2009)
	P06748	Nucleophosmin/B23	↓	6	6	2D-GE + MALDI-ToF-MS	Cochran et al (2003)
	P09874	Poly [ADP-ribose] polymerase 1	↑	1	1	ICAT + LC-MS/MS	Barnidge et al (2005)
	P05109	Protein S100-A8	↑	1	1	ICAT + LC-MS/MS	Barnidge et al (2005)
	P10768	S-formylglutathione hydrolase	↑	3	3	2D-DIGE + MALDI-ToF-MS + LC-MS/MS	Perrot et al (2011)
	P10768	S-formylglutathione hydrolase	↑	3	3	2D-DIGE + MALDI-ToF-MS + LC-MS/MS	Perrot et al (2011)
	Q86XK3	Swi5-dependent recombination DNA repair protein 1 homolog	↓	1	1	ICAT + LC-MS/MS	Barnidge et al (2005)
	Q8NBS9	Thioredoxin domain-containing protein 5	↓	1	1	ICAT + LC-MS/MS	Barnidge et al (2005)
	P67936	Tropomyosin alpha-4 chain	↓	6	22	iTRAQ + MALDI MS/MS	Alsagaby et al (2014)
	P08670	Vimentin	↓	1	1	ICAT + LC-MS/MS	Barnidge et al (2005)

**Supplementary Table S2. List of 274 proteins found by iTRAQ-based mass spectrometry to be significantly differentially expressed between M-CLL and UM-CLL samples ( $P < 0.05$ ).**

#	SwissProt Acc. No.	Name	Average no. of unique peptides (95%) $\pm$ SD	Average no. of peptides (95%)	Average % coverage (95)	Fold Change UM/M	<i>P</i>
1	Q92665	28S ribosomal protein S31, mitochondrial	4.0 $\pm$ 1.0	4.00	15.02	1.4	0.003
2	O95861	3'(2'),5'-biphosphate nucleotidase 1	5.3 $\pm$ 2.1	8.33	26.95	-2.3	0.006
3	Q96GC5	39S ribosomal protein L48, mitochondrial	1.5 $\pm$ 0.7	2.00	8.25	1.3	0.001
4	P18077	60S ribosomal protein L35a	1.3 $\pm$ 0.6	1.33	9.09	1.5	0.024
5	P62424	60S ribosomal protein L7a	2.7 $\pm$ 0.6	2.7	10.40	-1.3	0.017
6	Q01813	6-phosphofructokinase type C	17.7 $\pm$ 3.1	28.33	32.82	2.7	0.042
7	P68032	Actin, alpha cardiac muscle 1***	7	123.00	53.05	-1.5	0.011
8	P63261	Actin, cytoplasmic 2	67.0 $\pm$ 25.5	213.67	73.51	-2.7	0.014
9	O15143	Actin-related protein 2/3 complex subunit 1B	7.3 $\pm$ 2.9	9.67	21.33	-1.4	0.038
10	O15144	Actin-related protein 2/3 complex subunit 2	14.3 $\pm$ 2.1	21.33	48.11	-1.8	0.001
11	O15145	Actin-related protein 2/3 complex subunit 3	5.7 $\pm$ 2.5	12.67	38.02	-1.6	0.014
12	Q9BPX5	Actin-related protein 2/3 complex subunit 5-like protein	4.0 $\pm$ 1.0	4.67	32.90	-1.4	0.011
13	P61158	Actin-related protein 3	17.3 $\pm$ 4.0	28.00	53.43	-1.6	0.031
14	O95433	Activator of 90 kDa heat shock protein ATPase homolog 1	4.3 $\pm$ 1.2	5.67	19.23	1.6	0.026
15	Q9NPJ3	Acyl-coenzyme A thioesterase 13	2.0 $\pm$ 1.0	2.00	10.95	2.0	0.029
16	Q6P587	Acylpyruvase FAHD1, mitochondrial	1.3 $\pm$ 0.6	1.67	12.35	1.5	0.011
17	P55263	Adenosine kinase	8.3 $\pm$ 3.1	12.33	34.26	-3.0	0.007
18	Q01518	Adenylyl cyclase-associated protein 1	16.3 $\pm$ 3.5	30.33	37.40	-1.8	0.014
19	P62330	ADP-ribosylation factor 6	2.7 $\pm$ 0.6	2.67	20.00	-1.8	0.013
20	Q9NVJ2	ADP-ribosylation factor-like protein 8B	2.0 $\pm$ 1.0	4.33	23.84	-2.2	0.020
21	Q9Y2D5	A-kinase anchor protein 2	8.7 $\pm$ 5.5	10.00	14.67	2.0	0.001
22	P35611	Alpha-adducin	6.0 $\pm$ 2.6	7.33	12.66	-1.6	0.004

23	P61163	Alpha-centractin	4.7 ± 0.6	6.33	21.10	-1.4	0.012
24	Q01432	AMP deaminase 3	1.3 ± 0.6	1.33	2.17	-1.8	0.001
25	Q9H1A4	Anaphase-promoting complex subunit 1**	1	1.00	0.93	1.6	0.031
26	P04083	Annexin A1	9.7 ± 3.1	11.33	40.75	-2.8	0.011
27	P08758	Annexin A5	22.0 ± 3.5	44.33	72.71	2.6	0.006
28	P08133	Annexin A6	37.0 ± 5.2	66.67	62.36	-2.0	0.027
29	P63010	AP-2 complex subunit beta	11.3 ± 7.2	17.67	20.92	-1.5	0.010
30	Q96CW1	AP-2 complex subunit mu	1.3 ± 0.6	1.67	5.36	2.2	0.014
31	O14727	Apoptotic protease-activating factor 1	2.7 ± 1.2	2.67	2.75	-1.5	0.036
32	Q15057	Arf-GAP with coiled-coil, ANK repeat and PH domain-containing protein 2	4.3 ± 0.6	5.00	10.63	-1.3	0.036
33	Q99766	ATP synthase subunit s, mitochondrial	1.3 ± 0.6	1.67	6.82	-1.2	0.041
34	Q9NVI7	ATPase family AAA domain-containing protein 3A	6.3 ± 2.1	7.67	16.56	1.4	0.041
35	Q9UG63	ATP-binding cassette sub-family F member 2	1.0 ± 0.0	1.00	2.09	-1.2	0.023
36	O76031	ATP-dependent Clp protease ATP-binding subunit clpX-like, mitochondrial	2.7 ± 0.6	2.67	5.95	1.1	0.021
37	Q8NDB2	B-cell scaffold protein with ankyrin repeats	3.0 ± 1.7	3.67	6.88	-2.1	0.002
38	P16278	Beta-galactosidase	1.7 ± 1.2	1.67	3.59	-1.3	0.042
39	P55957	BH3-interacting domain death agonist	3.0 ± 1.0	3.33	20.34	-2.3	0.018
40	Q9Y6D6	Brefeldin A-inhibited guanine nucleotide-exchange protein 1	2.0 ± 0.0	2.00	1.14	-1.4	0.047
41	Q9UBW5	Bridging integrator 2	4.7 ± 1.5	5.33	14.40	-1.7	0.000
42	Q8IWX8	Calcium homeostasis endoplasmic reticulum protein	5.7 ± 2.3	6.67	9.35	1.4	0.034
43	Q8N4T8	Carbonyl reductase family member 4	2.3 ± 0.6	2.33	17.44	1.3	0.034
44	Q99467	CD180 antigen	4.0 ± 0.0	4.33	9.08	-1.5	0.014
45	P16070	CD44 antigen	4.3 ± 0.6	6.33	7.32	1.4	0.012
46	P30260	Cell division cycle protein 27 homolog***	1	2.00	2.55	-1.5	0.041
47	P62633	Cellular nucleic acid-binding protein	2.3 ± 1.5	3.00	16.95	1.3	0.027
48	Q9H444	Charged multivesicular body protein 4b	3.3 ± 2.1	4.00	22.47	-1.7	0.022

49	Q8NE62	Choline dehydrogenase, mitochondrial	4.0 ± 2.0	5.00	11.84	1.7	0.033
50	Q8N0X4	Citrate lyase subunit beta-like protein, mitochondrial	4.7 ± 0.6	6.00	22.06	-1.7	0.028
51	Q5T0F9	Coiled-coil and C2 domain-containing protein 1B	3.3 ± 2.1	3.67	4.70	-1.3	0.024
52	Q14011	Cold-inducible RNA-binding protein	5.0 ± 0.0	8.00	32.75	1.4	0.023
53	O14618	Copper chaperone for superoxide dismutase	3.3 ± 0.6	4.67	18.98	1.3	0.017
54	P31146	Coronin-1A	20.7 ± 4.9	33.33	42.66	-1.8	0.034
55	Q93034	Cullin-5***	2	2.00	2.44	-1.4	0.008
56	O14976	Cyclin-G-associated kinase	2.7 ± 1.5	2.67	3.08	-1.7	0.005
57	P00167	Cytochrome b5	1.7 ± 0.6	1.67	18.66	1.9	0.047
58	O43639	Cytoplasmic protein NCK2***	1.5 ± 0.7	1.50	5.26	-1.3	0.045
59	Q96KP4	Cytosolic non-specific dipeptidase	19.7 ± 4.2	32.50	55.37	-1.8	0.038
60	Q9BTC0	Death-inducer obliterator 1	7.0 ± 1.0	8.67	5.30	1.3	0.013
61	Q92608	Dedicator of cytokinesis protein 2	3.7 ± 1.2	4.00	2.71	-1.8	0.037
62	Q9BTZ2	Dehydrogenase/reductase SDR family member 4	4.0 ± 1.7	5.00	17.87	1.3	0.017
63	Q5QJE6	Deoxynucleotidyltransferase terminal-interacting protein 2	3.7 ± 3.1	4.00	7.89	1.3	0.003
64	P06746	DNA polymerase beta	1.3 ± 0.6	2.00	7.36	1.3	0.001
65	Q13426	DNA repair protein XRCC4**	1	1.00	5.06	1.4	0.040
66	P11387	DNA topoisomerase 1	14.3 ± 5.5	18.67	22.18	2.2	0.025
67	Q13422	DNA-binding protein Ikaros	1.7 ± 0.6	2.33	3.98	-1.6	0.049
68	O14593	DNA-binding protein RFXANK	1.5 ± 0.7	1.50	10.38	1.5	0.003
69	P78527	DNA-dependent protein kinase catalytic subunit	21.0 ± 8.9	23.00	7.11	-1.8	0.002
70	O15446	DNA-directed RNA polymerase I subunit RPA34	1.5 ± 0.7	1.50	7.55	1.8	0.017
71	P31689	DnaJ homolog subfamily A member 1	6.3 ± 1.2	8.00	26.03	-1.5	0.022
72	P25686	DnaJ homolog subfamily B member 2	1.3 ± 0.6	1.67	5.56	1.3	0.016
73	O75937	DnaJ homolog subfamily C member 8	5.0 ± 1.0	7.00	20.82	1.4	0.019

74	O60762	Dolichol-phosphate mannosyltransferase	1.7 ± 0.6	2.33	12.05	-1.2	0.044
75	Q02750	Dual specificity mitogen-activated protein kinase kinase 1	3.3 ± 1.5	4.33	12.13	-1.4	0.007
76	Q13627	Dual specificity tyrosine-phosphorylation-regulated kinase 1A	1.0 ± 0.0	1.67	2.58	-1.2	0.028
77	P50570	Dynamin-2	9.0 ± 2.6	9.67	13.41	-1.3	0.048
78	Q15075	Early endosome antigen 1	5.7 ± 2.5	7.00	5.34	-1.7	0.037
79	Q96C19	EF-hand domain-containing protein D2	7.3 ± 2.5	8.67	32.50	-2.0	0.049
80	O95163	Elongator complex protein 1*	1.0 ± 0.0	1.00	0.79	1.2	0.011
81	Q96DZ1	Endoplasmic reticulum lectin 1	2.5 ± 0.7	3.00	10.04	1.6	0.024
82	P30040	Endoplasmic reticulum resident protein 29	12.7 ± 2.5	22.00	54.53	1.6	0.013
83	P14625	Endoplasmin	33.3 ± 4.6	51.00	44.66	1.7	0.012
84	Q9NTX5	Enoyl-CoA hydratase domain-containing protein 1	4.3 ± 0.6	5.33	24.00	-1.3	0.038
85	P27105	Erythrocyte band 7 integral membrane protein***	3	3.00	16.67	-1.5	0.005
86	Q92506	Estradiol 17-beta-dehydrogenase 8	4.3 ± 1.2	6.33	24.40	1.3	0.027
87	O75822	Eukaryotic translation initiation factor 3 subunit J	2.0 ± 0.0	2.67	12.28	1.2	0.026
88	Q15024	Exosome complex component RRP42	6.0 ± 1.0	6.67	30.59	1.5	0.003
89	P52907	F-actin-capping protein subunit alpha-1	11.7 ± 1.5	36.67	58.51	-1.5	0.027
90	P47756	F-actin-capping protein subunit beta	9.7 ± 1.5	17.00	39.95	-1.3	0.040
91	Q92945	Far upstream element-binding protein 2	22.7 ± 3.2	42.67	42.47	1.5	0.019
92	Q9UNN5	FAS-associated factor 1	1.3 ± 0.6	1.67	3.44	-1.3	0.025
93	Q86UX7	Fermitin family homolog 3	14.7 ± 4.0	19.00	33.58	-1.9	0.014
94	P02675	Fibrinogen beta chain	8.0 ± 3.6	12.00	23.01	-6.0	0.049
95	P02679	Fibrinogen gamma chain	7.0 ± 1.4	7.50	15.68	-9.3	0.044
96	P21333	Filamin-A	81.7 ± 18.9	131.00	43.50	-3.0	0.006
97	O75369	Filamin-B	14.7 ± 4.7	21.67	9.72	2.4	0.000
98	Q5T1M5	FK506-binding protein 15	3.7 ± 0.6	4.33	4.46	-1.4	0.007
99	Q96GK7	Fumarylacetoacetate hydrolase domain-	2.3 ± 0.6	3.00	13.16	1.2	0.003

		containing protein 2A***					
100	Q06546	GA-binding protein alpha chain	6.7 ± 1.5	7.67	19.90	1.5	0.012
101	Q06547	GA-binding protein subunit beta-1	2.0 ± 1.7	2.00	3.80	1.3	0.002
102	Q9UEY8	Gamma-adducin	7.7 ± 1.5	9.00	17.66	-1.6	0.004
103	P17900	Ganglioside GM2 activator	2.0 ± 1.0	2.33	16.75	1.9	0.026
104	O14893	Gem-associated protein 2	1.0 ± 0.0	1.00	4.64	1.4	0.049
105	P11413	Glucose-6-phosphate 1-dehydrogenase	14.7 ± 3.2	20.67	40.45	-1.6	0.022
106	P07203	Glutathione peroxidase 1	10.0 ± 2.0	17.00	63.22	1.5	0.029
107	P00390	Glutathione reductase, mitochondrial	11.0 ± 3.5	13.67	33.78	-1.6	0.039
108	P09488	Glutathione S-transferase Mu 1	3.3 ± 0.6	5.33	23.55	-2.6	0.045
109	P41250	Glycyl-tRNA synthetase	7.0 ± 1.0	9.00	16.92	-1.5	0.013
110	Q08378	Golgin subfamily A member 3	10.0 ± 1.7	12.33	10.59	-1.6	0.018
111	P04899	Guanine nucleotide-binding protein G(i) subunit alpha-2	11.7 ± 3.1	18.00	49.58	-1.6	0.006
112	Q724V5	Hepatoma-derived growth factor-related protein 2	4.7 ± 0.6	7.00	11.87	1.8	0.003
113	Q99729	Heterogeneous nuclear ribonucleoprotein A/B	6.3 ± 0.6	10.67	23.59	1.4	0.039
114	P09651	Heterogeneous nuclear ribonucleoprotein A1	23.0 ± 6.1	57.00	46.15	1.7	0.022
115	P61978	Heterogeneous nuclear ribonucleoprotein K	25.3 ± 3.8	61.33	53.49	1.7	0.006
116	P16402	Histone H1.3	17.3 ± 11.5	58.33	50.68	-2.0	0.011
117	O43719	HIV Tat-specific factor 1	4.0 ± 1.7	4.33	9.45	1.3	0.018
118	P20036	HLA class II histocompatibility antigen, DP alpha 1 chain	5.7 ± 1.5	8.67	25.51	2.0	0.020
119	P01623†	Ig kappa chain V-III region***	4	4.00	35.32	81.1	0.047
120	P01871	Ig mu chain C region	11.3 ± 3.1	21.67	31.42	2.3	0.015
121	O14920	Inhibitor of nuclear factor kappa-B kinase subunit beta	2.7 ± 0.6	2.67	3.97	-1.3	0.017
122	Q8NBZ0	INO80 complex subunit E	1.7 ± 0.6	2.00	12.84	1.4	0.008
123	Q6PFW1	Inositol hexakisphosphate and diphosphoinositol-pentakisphosphate kinase 1***	2	2.00	1.74	-1.7	0.013

124	P20701	Integrin alpha-L	2.0 ± 0.0	2.00	2.62	-2.1	0.023
125	P11215	Integrin alpha-M	6.0 ± 4.4	6.33	7.09	-2.6	0.010
126	P05107	Integrin beta-2	6.3 ± 2.3	7.00	12.87	-2.3	0.046
127	Q9BWU0	Kanadaplin*	1.0 ± 0.0	1.00	2.01	1.2	0.018
128	Q07666	KH domain-containing, RNA-binding, signal transduction-associated protein 1	8.3 ± 2.1	11.00	17.38	1.6	0.026
129	O00139	Kinesin-like protein KIF2A	3.3 ± 3.2	3.67	5.57	-1.3	0.008
130	Q9Y2S2	Lambda-crystallin homolog	1.7 ± 1.2	1.67	6.17	-1.3	0.036
131	Q14696	LDLR chaperone MESD	2.7 ± 1.5	2.67	15.81	-1.3	0.048
132	O95232	Luc7-like protein 3	4.3 ± 1.2	8.00	14.35	1.5	0.004
133	Q9UJU2	Lymphoid enhancer-binding factor 1	2.3 ± 1.2	2.33	9.61	1.2	0.019
134	P42785	Lysosomal Pro-X carboxypeptidase	3.0 ± 1.0	3.33	10.49	1.5	0.021
135	P61626	Lysozyme C	3.0 ± 1.7	3.67	24.78	-3.9	0.003
136	P49137	MAP kinase-activated protein kinase 2*	1.0 ± 0.0	1.00	4.25	-1.4	0.043
137	O43312	Metastasis suppressor protein 1	3.0 ± 2.0	3.33	7.64	-1.8	0.029
138	O95983	Methyl-CpG-binding domain protein 3	1.3 ± 0.6	1.33	5.84	1.1	0.013
139	P27816	Microtubule-associated protein 4	9.0 ± 2.0	10.33	14.61	1.4	0.036
140	Q02978	Mitochondrial 2-oxoglutarate/malate carrier protein	2.0 ± 1.0	2.33	10.83	-1.5	0.010
141	O60220	Mitochondrial import inner membrane translocase subunit Tim8 A	1.7 ± 0.6	1.67	18.90	1.8	0.010
142	O94826	Mitochondrial import receptor subunit TOM70	7.3 ± 3.5	8.67	19.08	1.6	0.027
143	Q6NZ67	Mitotic-spindle organizing protein 2B	2.0 ± 0.0	2.00	22.15	1.4	0.001
144	O43148	mRNA cap guanine-N7 methyltransferase	3.7 ± 0.6	4.67	11.55	1.3	0.015
145	O00499	Myc box-dependent-interacting protein 1	5.0 ± 2.0	5.67	14.22	-1.6	0.004
146	Q9P2K5	Myelin expression factor 2***	2	2.00	5.83	1.4	0.016
147	P41218	Myeloid cell nuclear differentiation antigen	7.3 ± 2.5	13.33	20.80	-7.2	0.000
148	P05164	Myeloperoxidase	14.0 ± 7.8	17.33	23.98	-4.0	0.033
149	P60660	Myosin light polypeptide 6	11.7 ± 1.5	35.33	56.29	-1.8	0.023



150	P24844	Myosin regulatory light polypeptide 9	4.5 ± 3.5	14.00	56.40	-5.5	0.029
151	P35579	Myosin-9	95.0 ± 23.5	218.33	52.69	-2.9	0.002
152	B0I1T2	Myosin-Ig	6.0 ± 2.6	6.33	9.40	-1.9	0.005
153	Q13459	Myosin-IXb	2.3 ± 1.5	3.00	2.13	-1.4	0.036
154	P34059	N-acetylgalactosamine-6-sulfatase	2.0 ± 1.0	2.00	4.09	2.4	0.037
155	P41227	N-alpha-acetyltransferase 10	2.3 ± 0.6	2.67	13.05	-1.7	0.010
156	Q9BYT8	Neurolysin, mitochondrial	7.3 ± 1.5	9.33	13.59	1.8	0.023
157	Q15233	Non-POU domain-containing octamer-binding protein	17.0 ± 3.6	38.67	37.51	1.6	0.031
158	Q00653	Nuclear factor NF-kappa-B p100 subunit	3.3 ± 1.2	4.33	7.00	-1.3	0.035
159	O75376	Nuclear receptor corepressor 1	7.7 ± 3.8	7.67	4.69	1.3	0.026
160	Q9Y618	Nuclear receptor corepressor 2	1.7 ± 1.2	1.67	0.96	1.2	0.041
161	Q14978	Nucleolar and coiled-body phosphoprotein 1	4.7 ± 0.6	5.33	7.49	1.5	0.021
162	Q86U38	Nucleolar protein 9	1.3 ± 0.6	1.33	2.99	-2.3	0.035
163	Q9NQR4	Omega-amidase NIT2	7.3 ± 0.6	9.67	36.95	1.4	0.037
164	Q9BZF1	Oxysterol-binding protein-related protein 8	3.7 ± 1.5	3.67	5.66	-1.3	0.023
165	Q9NVE7	Pantothenate kinase 4	1.5 ± 0.7	1.50	2.39	1.4	0.035
166	Q96HC4	PDZ and LIM domain protein 5	1.0 ± 0.0	1.50	2.77	-1.5	0.008
167	Q13451	Peptidyl-prolyl cis-trans isomerase FKBP5	6.3 ± 2.1	6.67	21.74	1.8	0.050
168	Q8WUA2	Peptidyl-prolyl cis-trans isomerase-like 4	2.3 ± 1.5	2.33	7.18	1.2	0.035
169	P32119	Peroxiredoxin-2	6.0 ± 2.0	11.67	34.34	-2.1	0.029
170	P30044	Peroxiredoxin-5, mitochondrial	9.0 ± 0.0	17.00	47.20	1.6	0.018
171	P51659	Peroxisomal multifunctional enzyme type 2	17.3 ± 1.5	22.00	35.37	2.0	0.043
172	Q00325	Phosphate carrier protein, mitochondrial	3.0 ± 0.0	4.00	10.22	-1.4	0.025
173	Q9NTJ5	Phosphatidylinositide phosphatase SAC1	4.0 ± 1.7	5.00	10.45	-1.8	0.004
174	Q92835	Phosphatidylinositol 3,4,5-trisphosphate 5-phosphatase 1	14.3 ± 6.7	17.33	17.30	-1.4	0.037
175	P48426	Phosphatidylinositol 5-phosphate 4-kinase type-2 alpha	5.0 ± 1.0	6.00	16.42	-2.2	0.002
176	Q6P4A8	Phospholipase B-like 1	2.0 ± 0.0	2.00	2.80	-1.5	0.008

177	P36969	Phospholipid hydroperoxide glutathione peroxidase, mitochondrial	1.7 ± 0.6	1.67	10.83	-1.1	0.031
178	O60256	Phosphoribosyl pyrophosphate synthase-associated protein 2	9.7 ± 2.1	12.33	39.21	-1.4	0.047
179	Q8WU39	Plasma cell-induced resident endoplasmic reticulum protein	2.7 ± 0.6	3.33	24.16	3.4	0.024
180	P02776	Platelet factor 4	3.3 ± 1.5	6.00	40.59	-3.4	0.050
181	Q9H8W4	Pleckstrin homology domain-containing family F member 2	2.7 ± 0.6	2.67	16.47	-1.7	0.046
182	Q86U42	Polyadenylate-binding protein 2	4.7 ± 1.5	7.00	25.71	1.5	0.007
183	O95758	Polypyrimidine tract-binding protein 3***	1	3.00	6.88	-1.2	0.038
184	O75934	Pre-mRNA-splicing factor SPF27	3.3 ± 1.5	3.67	21.04	1.6	0.001
185	Q15007	Pre-mRNA-splicing regulator WTAP	1.5 ± 0.7	3.00	7.45	1.3	0.049
186	Q8NDH3	Probable aminopeptidase NPEPL1	1.3 ± 0.6	1.33	3.95	3.3	0.029
187	Q8IY21	Probable ATP-dependent RNA helicase DDX60	1.7 ± 1.2	2.33	1.44	-1.5	0.023
188	Q8WUM4	Programmed cell death 6-interacting protein	11.7 ± 2.1	14.67	20.70	-1.7	0.040
189	O75340	Programmed cell death protein 6	4.7 ± 0.6	5.67	34.21	-1.1	0.044
190	Q9HCU5	Prolactin regulatory element-binding protein	4.7 ± 1.5	4.67	21.42	1.4	0.013
191	Q01658	Protein Dr1*	1.0 ± 0.0	1.00	7.39	1.4	0.002
192	Q52LJ0	Protein FAM98B	9.7 ± 1.5	15.67	43.94	1.3	0.029
193	O94992	Protein HEXIM1	2.0 ± 1.0	2.67	6.31	-1.1	0.034
194	Q9Y316	Protein MEMO1	1.0 ± 0.0	1.00	5.05	-1.4	0.028
195	P29590	Protein PML	13.7 ± 4.2	17.00	21.24	1.5	0.030
196	Q96PU8	Protein quaking	2.0 ± 0.0	2.00	8.21	1.8	0.040
197	P05109	Protein S100-A8	2.3 ± 1.5	3.33	24.73	-6.3	0.001
198	P06702	Protein S100-A9	4.3 ± 3.1	7.67	47.66	-6.4	0.000
199	Q92734	Protein TFG	3.7 ± 0.6	4.33	12.83	1.4	0.022
200	O94979	Protein transport protein Sec31A	7.3 ± 1.2	10.33	9.97	1.4	0.022
201	Q14289	Protein-tyrosine kinase 2-beta	3.0 ± 1.7	3.33	5.05	-1.4	0.038
202	P0CB46	Putative caspase-16***	1	2.00	4.37	1.3	0.038

203	Q7Z7A4	PX domain-containing protein kinase-like protein**	1	1.00	3.63	-2.7	0.042
204	Q96GD0	Pyridoxal phosphate phosphatase	1.3 ± 0.6	1.33	6.08	-1.4	0.014
205	Q6K0P9	Pyrin and HIN domain-containing protein 1	5.7 ± 2.9	6.67	15.92	-3.0	0.009
206	Q9BXR0	Queuine tRNA-ribosyltransferase***	2	2.00	6.70	1.3	0.017
207	P50395	Rab GDP dissociation inhibitor beta	28.7 ± 2.3	45.00	69.06	-2.1	0.009
208	Q5R372	Rab GTPase-activating protein 1-like	3.0 ± 2.0	3.33	4.99	1.6	0.032
209	Q7LDG7	RAS guanyl-releasing protein 2	2.7 ± 0.6	3.33	8.10	-2.2	0.006
210	P61224	Ras-related protein Rap-1b	9.0 ± 1.7	13.33	59.96	-1.5	0.010
211	P08575	Receptor-type tyrosine-protein phosphatase C	35.3 ± 3.5	53.67	30.50	-1.7	0.009
212	P40937	Replication factor C subunit 5	1.7 ± 1.2	2.00	7.26	-1.2	0.025
213	Q8N264	Rho GTPase-activating protein 24	3.0 ± 0.0	3.67	5.84	1.3	0.010
214	Q92888	Rho guanine nucleotide exchange factor 1	12.0 ± 1.0	12.00	16.78	-1.5	0.049
215	P13489	Ribonuclease inhibitor	16.0 ± 2.0	32.67	50.25	1.5	0.030
216	P51812	Ribosomal protein S6 kinase alpha-3	5.3 ± 1.5	5.67	10.09	-1.5	0.006
217	Q9Y3A5	Ribosome maturation protein SBDS	2.0 ± 1.0	2.00	8.80	-1.3	0.034
218	Q9P2E9	Ribosome-binding protein 1	20.0 ± 1.7	22.67	23.88	3.1	0.000
219	Q9P2N5	RNA-binding protein 27	2.7 ± 1.5	3.67	3.84	-1.4	0.041
220	Q14498	RNA-binding protein 39	10.0 ± 1.7	12.00	26.98	1.3	0.012
221	Q9BWF3	RNA-binding protein 4	3.3 ± 2.3	4.33	18.68	1.1	0.044
222	Q9Y5S9	RNA-binding protein 8A	7.7 ± 1.5	13.00	57.66	1.3	0.006
223	Q01844	RNA-binding protein EWS	7.7 ± 1.2	15.00	15.80	1.4	0.011
224	Q6PCB5	Round spermatid basic protein 1-like protein*	1	1.00	2.01	1.2	0.038
225	Q9Y3Z3	SAM domain and HD domain-containing protein 1	5.3 ± 2.3	7.00	12.89	-3.6	0.001
226	Q13243	Serine/arginine-rich splicing factor 5	5.3 ± 0.6	6.33	23.29	1.3	0.025
227	Q8TD19	Serine/threonine-protein kinase Nek9	3.3 ± 0.6	3.67	4.66	-1.2	0.034
228	Q96QC0	Serine/threonine-protein phosphatase 1 regulatory subunit 10	4.0 ± 2.0	5.00	7.06	1.4	0.028
229	P60510	Serine/threonine-protein phosphatase 4	4.7 ± 1.5	5.33	24.11	1.4	0.020

		catalytic subunit					
230	Q96HS1	Serine/threonine-protein phosphatase PGAM5, mitochondrial	3.0 ± 0.0	3.00	9.69	-1.5	0.018
231	P50454	Serpin H1	4.0 ± 2.0	4.00	17.15	1.6	0.007
232	Q9BXP5	Serrate RNA effector molecule homolog	13.7 ± 3.1	16.67	20.93	1.3	0.029
233	P67812	Signal peptidase complex catalytic subunit SEC11A	2.0 ± 1.0	2.33	10.80	1.5	0.021
234	P37108	Signal recognition particle 14 kDa protein	4.7 ± 1.5	7.00	35.54	1.7	0.005
235	P49458	Signal recognition particle 9 kDa protein	4.3 ± 1.5	8.00	50.78	1.8	0.018
236	P42229	Signal transducer and activator of transcription 5A	5.3 ± 2.1	5.67	7.81	-1.9	0.028
237	O43166	Signal-induced proliferation-associated 1-like protein 1	1.5 ± 0.7	1.50	1.00	-1.3	0.004
238	P62316	Small nuclear ribonucleoprotein Sm D2	5.0 ± 1.7	12.67	43.50	1.3	0.039
239	P30626	Sorcin	6.3 ± 1.5	9.67	38.05	1.5	0.013
240	P23246	Splicing factor, proline- and glutamine-rich	22.3 ± 5.7	41.00	33.29	1.7	0.003
241	Q9UBE0	SUMO-activating enzyme subunit 1	9.0 ± 0.0	12.67	36.61	1.5	0.010
242	Q969G3	SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily E member 1	5.7 ± 3.2	8.33	22.06	1.5	0.039
243	O43760	Synaptogyrin-2	2.0 ± 0.0	2.33	8.93	-1.2	0.019
244	O95721	Synaptosomal-associated protein 29	2.3 ± 1.5	2.67	11.50	1.3	0.020
245	Q15833	Syntaxin-binding protein 2	3.0 ± 1.0	3.00	8.82	-1.2	0.030
246	O00186	Syntaxin-binding protein 3	4.0 ± 0.0	4.00	6.67	-1.3	0.047
247	Q9Y490	Talin-1	76.3 ± 8.7	143.00	46.14	-3.5	0.015
248	P56279	T-cell leukemia/lymphoma protein 1A	5.0 ± 1.7	6.33	47.37	2.9	0.004
249	Q99832	T-complex protein 1 subunit eta	12.7 ± 2.3	15.33	34.25	-1.5	0.041
250	O95801	Tetratricopeptide repeat protein 4***	1	2.00	7.24	-1.3	0.048
251	Q8NBS9	Thioredoxin domain-containing protein 5	20.0 ± 4.6	34.00	48.77	3.2	0.007
252	Q6I9Y2	THO complex subunit 7 homolog	1.3 ± 0.6	1.33	7.03	1.6	0.037
253	P07996	Thrombospondin-1	9.7 ± 6.7	12.00	11.17	-5.2	0.017

254	Q9Y2W1	Thyroid hormone receptor-associated protein 3	11.3 ± 0.6	13.33	15.04	1.7	0.008
255	P52655	Transcription initiation factor IIA subunit 1	2.0 ± 0.0	3.00	7.45	1.2	0.040
256	Q13263	Transcription intermediary factor 1-beta	21.7 ± 4.0	36.67	35.57	1.5	0.012
257	Q92973	Transportin-1	3.3 ± 1.2	3.33	5.16	-2.2	0.029
258	Q96G46	tRNA-dihydrouridine(47) synthase [NAD(P)(+)]-like	2.7 ± 1.2	2.67	7.33	-1.3	0.036
259	Q9NYL9	Tropomodulin-3	5.3 ± 3.1	5.67	26.61	-1.5	0.026
260	P55327	Tumor protein D52	4.3 ± 1.5	7.00	27.08	-3.9	0.000
261	P41240	Tyrosine-protein kinase CSK	13.0 ± 2.6	20.00	35.19	-1.5	0.050
262	P29350	Tyrosine-protein phosphatase non-receptor type 6	24.0 ± 6.2	40.00	50.81	-2.6	0.001
263	P08621	U1 small nuclear ribonucleoprotein 70 kDa	5.3 ± 2.1	6.67	16.85	1.2	0.029
264	Q13107	Ubiquitin carboxyl-terminal hydrolase 4	3.0 ± 1.7	3.67	4.60	-1.3	0.047
265	O94888	UBX domain-containing protein 7	3.3 ± 1.5	4.00	9.88	1.3	0.049
266	Q9NYU2	UDP-glucose:glycoprotein glucosyltransferase 1	19.3 ± 3.2	23.00	17.45	-1.6	0.010
267	Q9BQA9	Uncharacterized protein C17orf62***	2.0 ± 1.4	3.50	11.23	-1.6	0.032
268	Q6ICL3	Uncharacterized protein C22orf25*	1.0 ± 0.0	1.00	6.88	-1.6	0.031
269	Q86YS7	Uncharacterized protein KIAA0528**	1	1.00	2.00	1.9	0.046
270	P54727	UV excision repair protein RAD23 homolog B	7.7 ± 2.1	12.67	24.04	1.4	0.029
271	Q709C8	Vacuolar protein sorting-associated protein 13C	20.7 ± 4.2	21.67	7.72	-1.4	0.014
272	O75351	Vacuolar protein sorting-associated protein 4B	6.3 ± 0.6	7.00	20.42	-1.4	0.026
273	P50552	Vasodilator-stimulated phosphoprotein	7.3 ± 2.1	8.67	24.91	-1.8	0.050
274	P49750	YLP motif-containing protein 1	9.0 ± 5.0	10.00	6.25	1.2	0.002

All proteins identified by ≥2 peptides at ≥90% confidence and present in ≥2 iTRAQ experiments unless stated.

- \* Proteins identified by a single peptide (≥99% confidence) in ≥2 iTRAQ experiments
- \*\* Proteins identified by a single peptide (≥99% confidence) in a single iTRAQ experiment
- \*\*\* Proteins identified by ≥2 peptides (≥90% confidence) in a single iTRAQ experiment
- † See also P04206, P01623, P01620, P18136, P18135

**Supplementary Table S3. List of 169 signalling pathways which were significantly enriched ( $P<0.05$ ) by the GeneGo Pathway Maps in the Metacore database using 274 proteins that were significantly differentially expressed between UM-CLL and M-CLL ( $P<0.05$ )**

	Enriched pathway map	<i>P</i> value	FDR	No. of diff exp. proteins in pathway	Total proteins in pathway
1	Cytoskeleton remodeling_Regulation of actin cytoskeleton by Rho GTPases	<0.001	0.00	7	23
2	Blood coagulation_GPCRs in platelet aggregation	<0.001	0.00	10	71
3	Chemotaxis_Inhibitory action of lipoxins on IL-8- and Leukotriene B4-induced neutrophil migration	<0.001	0.00	8	51
4	Inhibitory action of Lipoxins on neutrophil migration	<0.001	0.00	8	57
5	Cell adhesion_Chemokines and adhesion	<0.001	0.00	10	100
6	wtCFTR and delta508 traffic / Clathrin coated vesicles formation (norm and CF)	<0.001	0.00	5	19
7	Cell adhesion_IL-8-dependent cell migration and adhesion	<0.001	0.00	6	33
8	Transport_Clathrin-coated vesicle cycle	<0.001	0.00	8	71
9	Chemotaxis_Leukocyte chemotaxis	<0.001	0.00	8	75
10	Blood coagulation_GPIb-IX-V-dependent platelet activation	<0.001	0.00	8	76
11	Immune response_Immunological synapse formation	<0.001	0.00	7	59
12	Cell adhesion_Histamine H1 receptor signaling in the interruption of cell barrier integrity	<0.001	0.00	6	45
13	Development_G-CSF-induced myeloid differentiation	<0.001	0.00	5	30
14	Cytoskeleton remodeling_Integrin outside-in signaling	<0.001	0.00	6	49
15	Cytoskeleton remodeling_Cytoskeleton remodeling	<0.001	0.00	8	102
16	LRRK2 in neurons in Parkinson's disease	<0.001	0.00	5	33
17	Immune response_CCR3 signaling in eosinophils	<0.001	0.00	7	77
18	CCR4-dependent immune cell chemotaxis in asthma and atopic dermatitis	<0.001	0.00	5	34
19	Development_S1P1 receptor signaling via beta-arrestin	<0.001	0.00	5	34
20	Chemotaxis_CCR4-induced chemotaxis of immune cells	<0.001	0.00	5	34
21	Mechanism of action of CCR4 antagonists in asthma and atopic dermatitis (Variant 1)	<0.001	0.00	5	34
22	Immune response_CXCR4 signaling via second messenger	<0.001	0.00	5	34
23	Airway smooth muscle contraction in asthma	<0.001	0.00	6	56
24	Gamma-secretase regulation of osteogenesis	<0.001	0.00	5	37
25	Development_MAG-dependent inhibition of neurite outgrowth	<0.001	0.00	5	37
26	Immune response_Role of integrins in NK cells cytotoxicity	<0.001	0.00	5	38
27	Transcription_Sin3 and NuRD in transcription regulation	<0.001	0.00	5	38

28	Immune response_Neutrotensin-induced activation of IL-8 in colonocytes	<0.001	0.00	5	42
29	Chemotaxis_C5a-induced chemotaxis	<0.001	0.00	5	43
30	Development_Mu-type opioid receptor signaling via Beta-arrestin	<0.001	0.00	4	24
31	Immune response_MIF-induced cell adhesion, migration and angiogenesis	<0.001	0.01	5	46
32	Chemotaxis_Lipoxin inhibitory action on fMLP-induced neutrophil chemotaxis	<0.001	0.01	5	46
33	Muscle contraction_Delta-type opioid receptor in smooth muscle contraction	<0.001	0.01	4	26
34	Development_S1P2 and S1P3 receptors in cell proliferation and differentiation	<0.001	0.01	4	26
35	Cell adhesion_Integrin-mediated cell adhesion and migration	<0.001	0.01	5	48
36	Development_Thromboxane A2 pathway signaling	0.001	0.01	5	49
37	Immune response_IL-2 activation and signaling pathway	0.001	0.01	5	49
38	Immune response_Signaling pathway mediated by IL-6 and IL-1	0.001	0.01	4	30
39	Cytoskeleton remodeling_TGF, WNT and cytoskeletal remodeling	0.001	0.01	7	111
40	Immune response_IL-3 activation and signaling pathway	0.001	0.01	4	31
41	Immune response_CCL2 signaling	0.001	0.01	5	54
42	CFTR folding and maturation (norm and CF)	0.001	0.01	3	14
43	Development_Transcription regulation of granulocyte development	0.001	0.01	4	32
44	Muscle contraction_GPCRs in the regulation of smooth muscle tone	0.001	0.01	6	83
45	Cell adhesion_Integrin inside-out signaling	0.001	0.01	5	56
46	Chemotaxis_CXCR4 signaling pathway	0.001	0.01	4	34
47	Development_EPO-induced Jak-STAT pathway	0.001	0.01	4	35
48	Immune response_Regulation of T cell function by CTLA-4	0.001	0.01	4	36
49	Development_c-Kit ligand signaling pathway during hemopoiesis	0.001	0.01	5	61
50	Cell adhesion_Role of tetraspanins in the integrin-mediated cell adhesion	0.002	0.02	4	37
51	Transcription_NF-kB signaling pathway	0.002	0.02	4	39
52	Cytoskeleton remodeling_Alpha-1A adrenergic receptor-dependent inhibition of PI3K	0.002	0.02	3	19
53	Cytoskeleton remodeling_Role of PKA in cytoskeleton reorganisation	0.002	0.02	4	40
54	Immune response_CD16 signaling in NK cells	0.002	0.02	5	69
55	Apoptosis and survival_Anti-apoptotic TNFs/NF-kB/Bcl-2 pathway	0.002	0.02	4	42
56	Apoptosis and survival_Lymphotoxin-beta receptor signaling	0.002	0.02	4	42
57	Glutathione metabolism / Rodent version	0.003	0.02	5	70
58	Development_ACM2 and ACM4 activation of ERK	0.003	0.02	4	43
59	Apoptosis and survival_TNFR1 signaling pathway	0.003	0.02	4	43
60	Development_S1P3 receptor signaling pathway	0.003	0.02	4	43
61	Development_Flt3 signaling	0.003	0.02	4	44

62	Immune response_IL-5 signalling	0.003	0.02	4	44
63	LRRK2 and immune function in Parkinson's disease	0.003	0.03	3	22
64	Immune response_Fc gamma R-mediated phagocytosis in macrophages	0.003	0.03	4	46
65	Regulation of metabolism_Triiodothyronine and Thyroxine signaling	0.004	0.03	4	48
66	Muscle contraction_Relaxin signaling pathway	0.004	0.03	4	48
67	Development_Glucocorticoid receptor signaling	0.004	0.03	3	24
68	Development_GDNF signaling	0.004	0.03	3	24
69	Development_A3 receptor signaling	0.004	0.03	4	49
70	Development_GM-CSF signaling	0.005	0.03	4	50
71	Development_EDNRB signaling	0.005	0.03	4	50
72	Immune response_C5a signaling	0.005	0.03	4	50
73	Development_TGF-beta receptor signaling	0.005	0.03	4	50
74	Signal transduction_Activation of PKC via G-Protein coupled receptor	0.005	0.04	4	52
75	G-protein signaling_Proinsulin C-peptide signaling	0.005	0.04	4	52
76	Development_VEGF signaling via VEGFR2 - generic cascades	0.006	0.04	5	84
77	Development_A1 receptor signaling	0.006	0.04	4	53
78	Immune response_T cell receptor signaling pathway	0.006	0.04	4	53
79	Development_WNT signaling pathway. Part 2	0.006	0.04	4	53
80	Immune response_BCR pathway	0.006	0.04	4	54
81	Blood coagulation_GPVI-dependent platelet activation	0.007	0.04	4	55
82	Proteolysis_Putative SUMO-1 pathway	0.007	0.04	3	29
83	Chemotaxis_CCL2-induced chemotaxis	0.007	0.04	4	56
84	Muscle contraction_S1P2 receptor-mediated smooth muscle contraction	0.008	0.04	3	30
85	Apoptosis and survival_Granzyme A signaling	0.008	0.04	3	30
86	Development_Osteopontin signaling in osteoclasts	0.008	0.04	3	30
87	Cytoskeleton remodeling_RalA regulation pathway	0.008	0.04	3	30
88	Immune response_CCR5 signaling in macrophages and T lymphocytes	0.008	0.04	4	58
89	Regulation of CFTR activity (norm and CF)	0.008	0.04	4	58
90	Immune response_ETV3 affect on CSF1-promoted macrophage differentiation	0.008	0.05	3	31
91	Cytoskeleton remodeling_Reverse signaling by ephrin B	0.008	0.05	3	31
92	Development_Alpha-2 adrenergic receptor activation of ERK	0.010	0.05	4	62
93	Development_Angiotensin activation of ERK	0.010	0.05	3	33
94	Cell adhesion_Alpha-4 integrins in cell migration and adhesion	0.011	0.06	3	34
95	Development_NOTCH1-mediated pathway for NF-KB activity modulation	0.011	0.06	3	34



96	Immune response_Sialic-acid receptors (Siglecs) signaling	0.011	0.06	2	12
97	Transport_Macropinocytosis	0.011	0.06	2	12
98	Glutathione metabolism	0.011	0.06	4	64
99	Glutathione metabolism / Human version	0.012	0.06	4	65
100	G-protein signaling_S1P2 receptor signaling	0.012	0.06	3	35
101	Development_SSTR2 in regulation of cell proliferation	0.013	0.06	3	36
102	Development_Activation of ERK by Kappa-type opioid receptor	0.013	0.06	3	36
103	Cell adhesion_Tight junctions	0.013	0.06	3	36
104	Delta508-CFTR traffic / ER-to-Golgi in CF	0.013	0.06	2	13
105	Normal wtCFTR traffic / ER-to-Golgi	0.013	0.06	2	13
106	Development_Beta-adrenergic receptors transactivation of EGFR	0.014	0.06	3	37
107	Immune response_IL-7 signaling in T lymphocytes	0.015	0.07	3	38
108	Apoptosis and survival_APRIL and BAFF signaling	0.016	0.07	3	39
109	Development_PACAP signaling in neural cells	0.016	0.07	3	39
110	G-protein signaling_Regulation of p38 and JNK signaling mediated by G-proteins	0.016	0.07	3	39
111	Regulation of lipid metabolism_Stimulation of Arachidonic acid production by ACM receptors	0.017	0.08	4	72
112	Neurophysiological process_ACM1 and ACM2 in neuronal membrane polarization	0.017	0.08	3	40
113	Reproduction_Progesterone-mediated oocyte maturation	0.017	0.08	3	40
114	Immune response_PIP3 signaling in B lymphocytes	0.019	0.08	3	42
115	Development_Growth hormone signaling via PI3K/AKT and MAPK cascades	0.019	0.08	3	42
116	Gamma-secretase proteolytic targets	0.020	0.09	4	76
117	Immune response_IL-7 signaling in B lymphocytes	0.021	0.09	3	43
118	Immune response_HTR2A-induced activation of cPLA2	0.021	0.09	3	43
119	Apoptosis and survival_TNF-alpha-induced Caspase-8 signaling	0.021	0.09	3	43
120	Development_A2A receptor signaling	0.021	0.09	3	43
121	Development_VEGF signaling and activation	0.021	0.09	3	43
122	Immune response_IL-4 signaling pathway	0.022	0.09	3	44
123	Development_Activation of Erk by ACM1, ACM3 and ACM5	0.022	0.09	3	44
124	Development_S1P1 signaling pathway	0.022	0.09	3	44
125	DNA damage_Role of SUMO in p53 regulation	0.022	0.09	2	17
126	Transcription_Androgen Receptor nuclear signaling	0.023	0.09	3	45
127	Development_G-Proteins mediated regulation MAPK-ERK signaling	0.025	0.10	3	46
128	Development_GDNF family signaling	0.025	0.10	3	46
129	Development_Endothelin-1/EDNRA transactivation of EGFR	0.025	0.10	3	46

130	Transport_Alpha-2 adrenergic receptor regulation of ion channels	0.026	0.10	3	47
131	Development_Beta-adrenergic receptors regulation of ERK	0.026	0.10	3	47
132	DNA damage_NHEJ mechanisms of DSBs repair	0.027	0.10	2	19
133	Development_G-CSF signaling	0.029	0.11	3	49
134	Apoptosis and survival_HTR1A signaling	0.031	0.11	3	50
135	Mucin expression in CF via TLRs, EGFR signaling pathways	0.031	0.11	3	50
136	wtCFTR and delta508-CFTR traffic / Generic schema (norm and CF)	0.031	0.11	3	50
137	Development_A2B receptor: action via G-protein alpha s	0.031	0.11	3	50
138	Cell cycle_Chromosome condensation in prometaphase	0.033	0.12	2	21
139	Development_IGF-1 receptor signaling	0.034	0.12	3	52
140	Apoptosis and survival_Endoplasmic reticulum stress response pathway	0.035	0.12	3	53
141	Development_Endothelin-1/EDNRA signaling	0.035	0.12	3	53
142	Immune response_HMGB1/RAGE signaling pathway	0.035	0.12	3	53
143	Development_S1P4 receptor signaling pathway	0.036	0.12	2	22
144	Cell cycle_Sister chromatid cohesion	0.036	0.12	2	22
145	Amitraz-induced inhibition of Insulin secretion	0.036	0.12	2	22
146	Development_Thrombopoetin signaling via JAK-STAT pathway	0.036	0.12	2	22
147	Immune response_Role of DAP12 receptors in NK cells	0.037	0.12	3	54
148	Immune response_HSP60 and HSP70/ TLR signaling pathway	0.037	0.12	3	54
149	NRF2 regulation of oxidative stress response	0.037	0.12	3	54
150	Immune response_IL-12 signaling pathway	0.039	0.13	2	23
151	Immune response_IL-15 signaling via JAK-STAT cascade	0.039	0.13	2	23
152	Delta508-CFTR traffic / Sorting endosome formation in CF	0.039	0.13	2	23
153	Development_Delta- and kappa-type opioid receptors signaling via beta-arrestin	0.039	0.13	2	23
154	PGE2 pathways in cancer	0.039	0.13	3	55
155	Immune response_Fc epsilon RI pathway	0.039	0.13	3	55
156	Immune response_IFN alpha/beta signaling pathway	0.042	0.13	2	24
157	Immune response_IL-27 signaling pathway	0.042	0.13	2	24
158	Development_Dopamine D2 receptor transactivation of EGFR	0.042	0.13	2	24
159	Immune response_IL-33 signaling pathway	0.043	0.13	3	57
160	Development_Prolactin receptor signaling	0.044	0.14	3	58
161	Cell cycle_Initiation of mitosis	0.045	0.14	2	25
162	G-protein signaling_TC21 regulation pathway	0.045	0.14	2	25
163	G-protein signaling_R-RAS regulation pathway	0.045	0.14	2	25

164	Apoptosis and survival_Apoptotic Activin A signaling	0.045	0.14	2	25
165	Development_Angiotensin signaling via beta-Arrestin	0.045	0.14	2	25
166	Immune response_IL-18 signaling	0.048	0.14	3	60
167	Immune response_IL-17 signaling pathways	0.048	0.14	3	60
168	Cell adhesion_Cadherin-mediated cell adhesion	0.049	0.14	2	26
169	Development_Cross-talk between VEGF and Angiopoietin 1 signaling pathways	0.049	0.14	2	26

## 1. Supplementary figure legends.

### **Supplementary Figure S1. Verification of differential protein expression by Western blotting.** (A)

Lysates from all 9 M-CLL and 9 UM-CLL samples were subjected to immunoblotting for 3 proteins found by iTRAQ-MS to be differentially expressed with  $P$  values of  $<0.001$  (MNDA 50kDa; P41218), 0.019 (LEF-1 48kDa and  $\Delta$ LEF-1 38kDa; Q9UJU2) and 0.004 (TCL-1 14kDa; P56279). (B) Two-tailed Mann Whitney  $U$ -tests were used to determine statistical differences between the median values of optical density, normalised against  $\beta$ -actin, for UM-CLL and M-CLL samples. MNDA, LEF-1 and TCL-1 were all found to be differentially expressed by immunoblotting with  $P$  values of 0.011, 0.004 and 0.024, respectively. In keeping with the iTRAQ-MS data, levels of LEF-1 and TCL-1 were higher in UM-CLL whereas levels of MNDA were lower.

### **Supplementary Figure S2. PANTHER classification of differentially expressed proteins.** Proteins

found to be differentially expressed between UM-CLL and M-CLL ( $p < 0.05$ ) were categorised by their molecular functions using the PANTHER classification system. (A) Pie chart of Gene Ontology (GO) molecular functions of the 127 proteins which were expressed at a higher level in UM-CLL showing that 38% of these proteins were involved in binding and 35% in catalytic activity. (B) Pie chart of GO molecular functions of the 147 proteins which were expressed at a lower level in UM-CLL showing that 33% of these proteins were involved in binding and 29% in catalytic activity. A greater number of proteins under-expressed in UM-CLL cells were involved in structural molecule activity (GO:0005198) (compare 17% in b to 6% in a). 96% of the proteins involved in structural molecular activity that were under-expressed in UM-CLL cells were associated with structural components of the cytoskeleton (GO:0005200), whereas 86% of the proteins involved in structural molecular activity that were over-expressed in UM-CLL cells were associated with structural components of the ribosome (GO:0003735) (data not shown). (C) Bar charts showing the specific binding (GO:0005488) and catalytic (GO:0003824) functions associated with proteins expressed at higher levels in UM-CLL cells. The majority of these proteins are involved in nucleic acid binding and RNA splicing factors activity suggesting higher levels of transcriptional and translational activities in UM-CLL cells. (D) Bar chart showing the binding and catalytic functions associated with proteins expressed at lower levels in UM-CLL cells. The majority of these proteins are involved in protein binding (mostly to cytoskeletal proteins (GO:0008092) (data not shown)) and transferase activity.

### **Supplementary Figure S3. Functional analysis of CCL21/CCR7-mediated migration.** (A) Thirty CLL

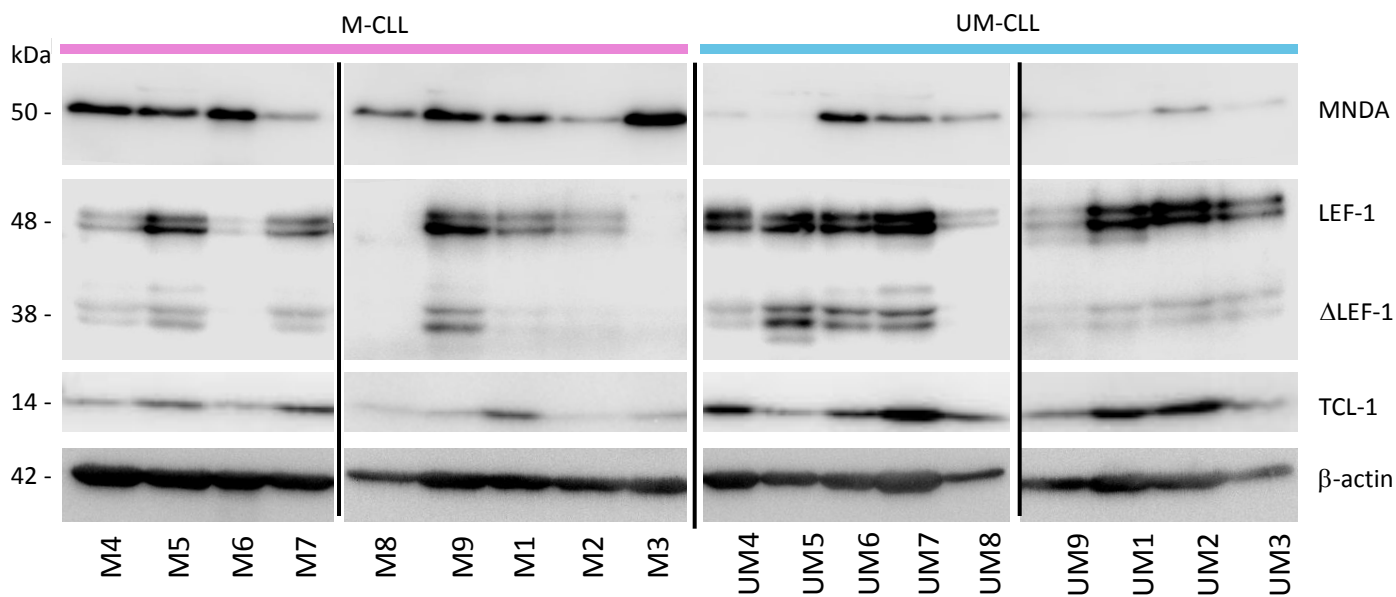
samples (15 UM-CLL and 15 M-CLL) were tested for their ability to migrate towards CCL21 using in-vitro transwell assays. For each case, the result was taken as the average of three technical replicates. The median migration index of M-CLL and UM-CLL cells were 25 and 15, respectively

(grand median of 16.3). (B) Surface expression of the CCL21 receptor, CCR7, was measured by flow cytometry. The receptor was expressed at similar levels on M-CLL and UM-CLL samples.

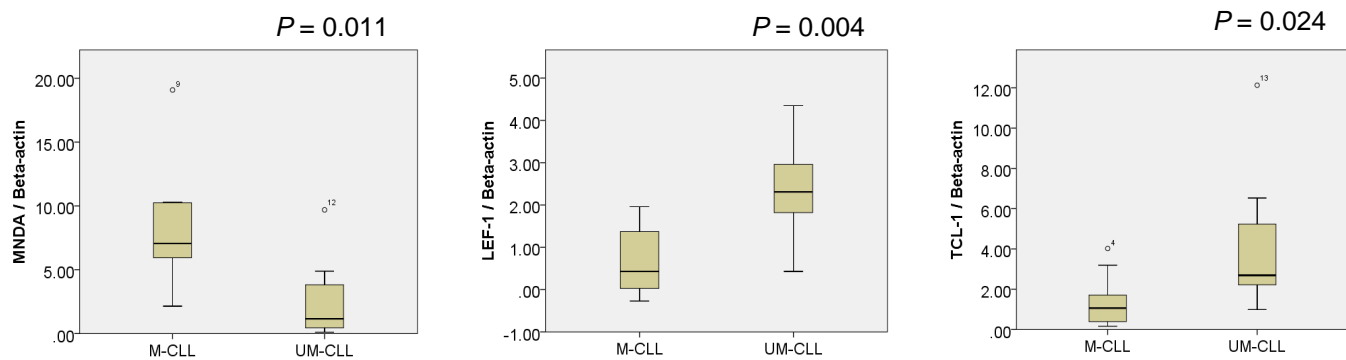
**Supplementary Figure S4. Enrichment of the BCR immune response pathway by proteins differentially expressed in M-CLL versus UM-CLL.** GeneGo pathway analysis showed that the immune response pathway involving BCR signalling was significantly enriched ( $P=0.006$ ) by proteins differentially expressed between UM-CLL and M-CLL. Within this pathway, immunoglobulin  $\mu$  heavy chain C region (IGHM, P01871) was expressed at higher levels in UM-CLL compared to M-CLL samples ( $P=0.015$ ), whereas two cellular inhibitors of Lyn, receptor-type tyrosine-protein phosphatase C (CD45, P08575) and tyrosine-protein phosphatase non-receptor type 6 (SHP-1, P29350), were under-expressed ( $P$  values of 0.009 and 0.001, respectively).

**Supplementary Figure S5. Enrichment of the Endoplasmic reticulum stress response pathway (apoptosis and survival) by proteins differentially expressed in M-CLL versus UM-CLL.** GeneGo pathway analysis showed that the ER stress response pathway was significantly enriched ( $P=0.035$ ) by proteins differentially expressed between UM-CLL and M-CLL. Within this pathway endoplasmic reticulum chaperone protein (P14625), which stimulates protein folding and thereby protects cells against apoptosis triggered by the unfolded protein response, was over-expressed in UM-CLL cells ( $P=0.012$ ). Furthermore, the pro-apoptotic molecules BH3-interacting domain death agonist (BID, P55957) and apoptotic protease-activating factor 1 (APAF1, O14727), were both expressed at significantly lower levels in UM-CLL cells ( $P$  values of 0.018 and 0.036, respectively).

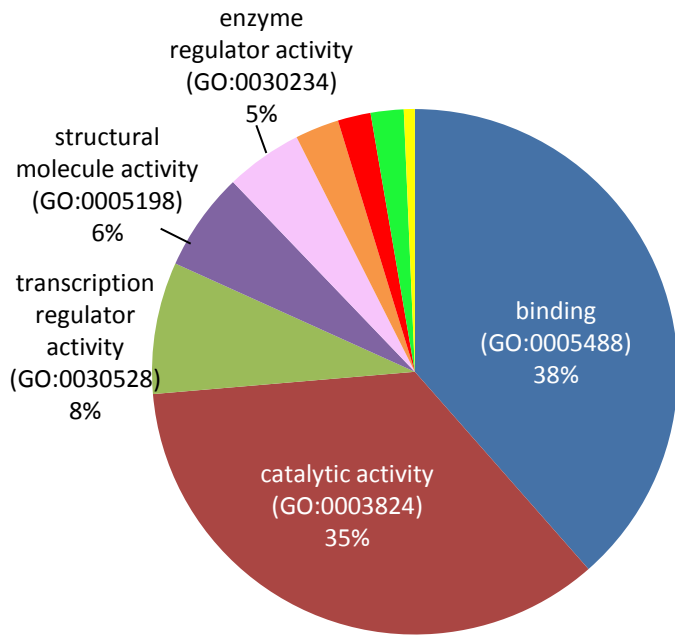
A



B

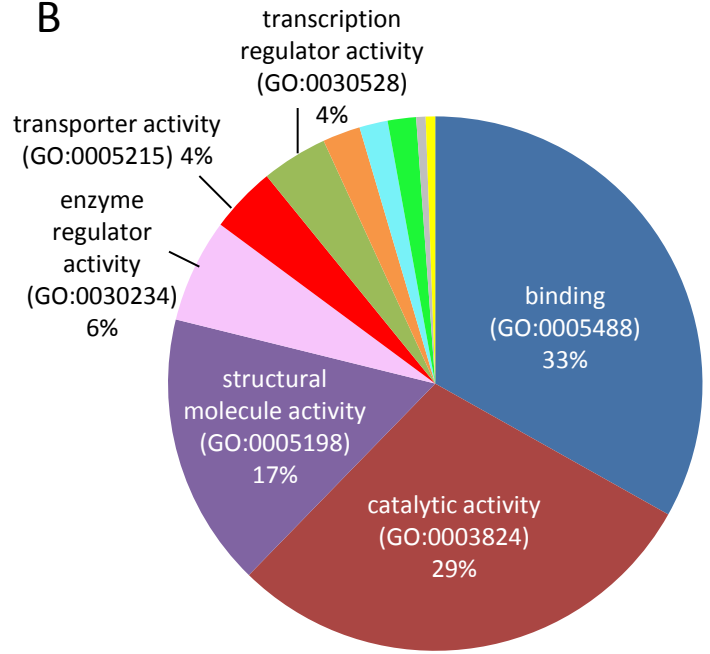


A



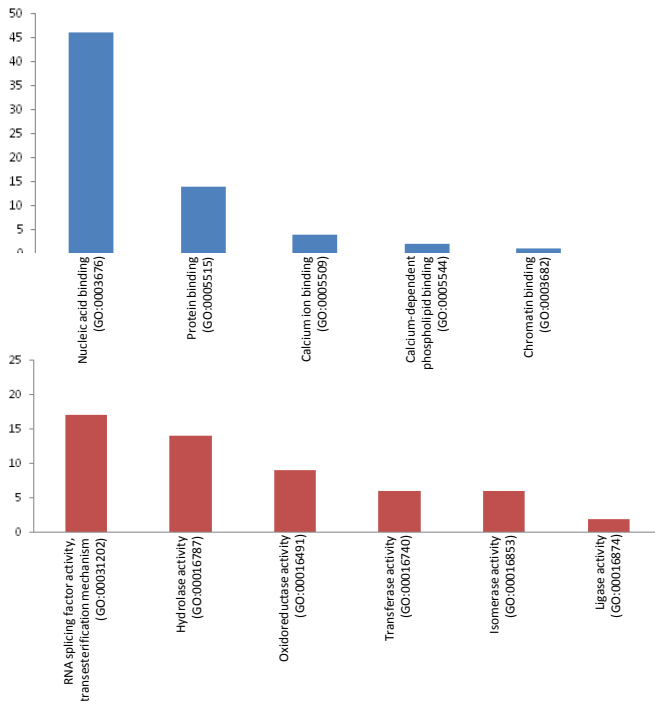
Molecular functions of proteins with significantly higher levels of expression in UM-CLL

B



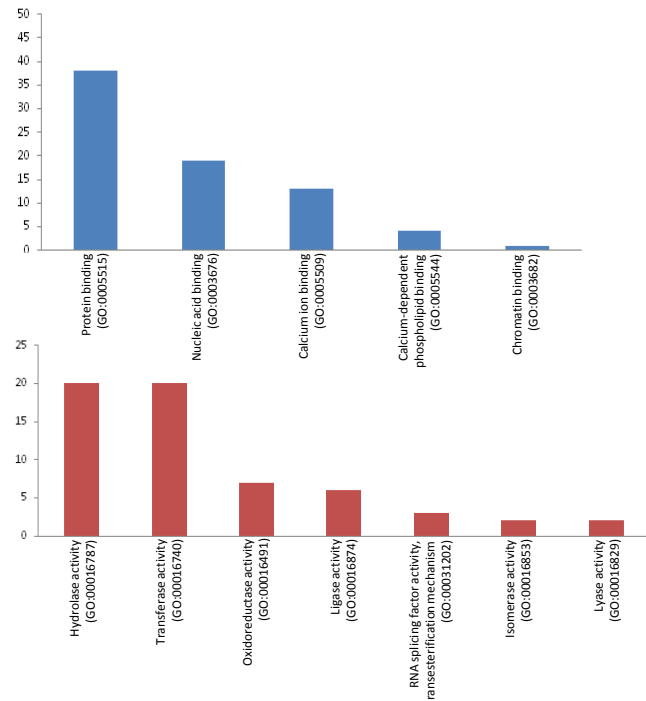
Molecular functions of proteins with significantly lower levels of expression in UM-CLL

C



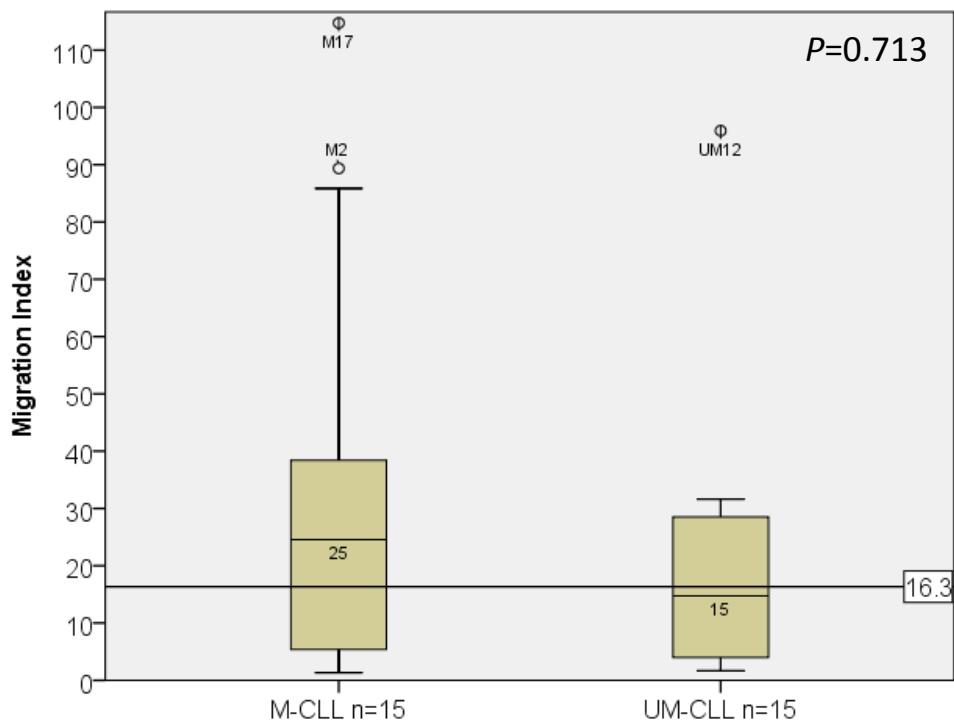
Binding and catalytic activities of proteins with significantly higher levels of expression in UM-CLL

D



Binding and catalytic activities of proteins with significantly lower levels of expression in UM-CLL

A

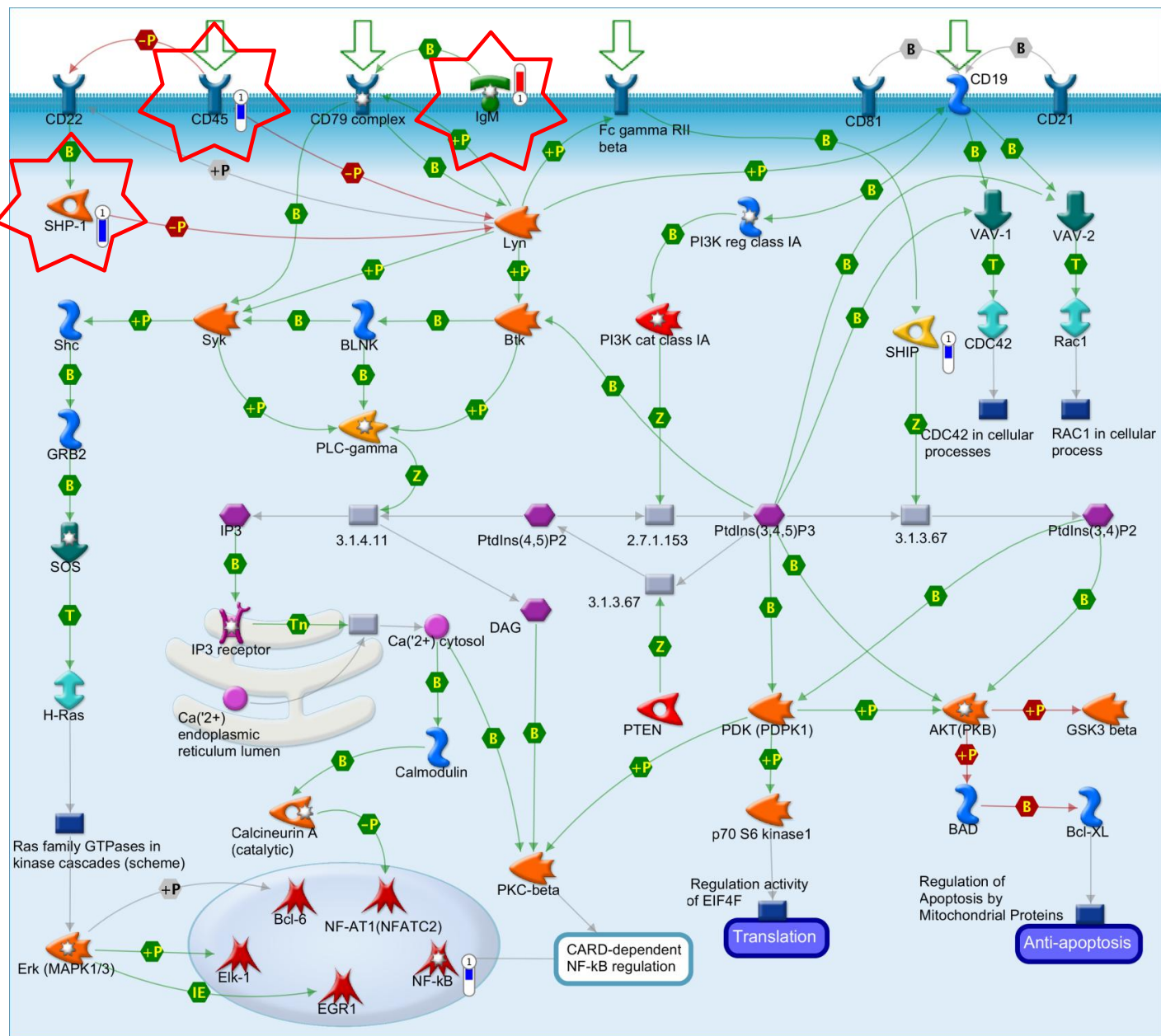


B





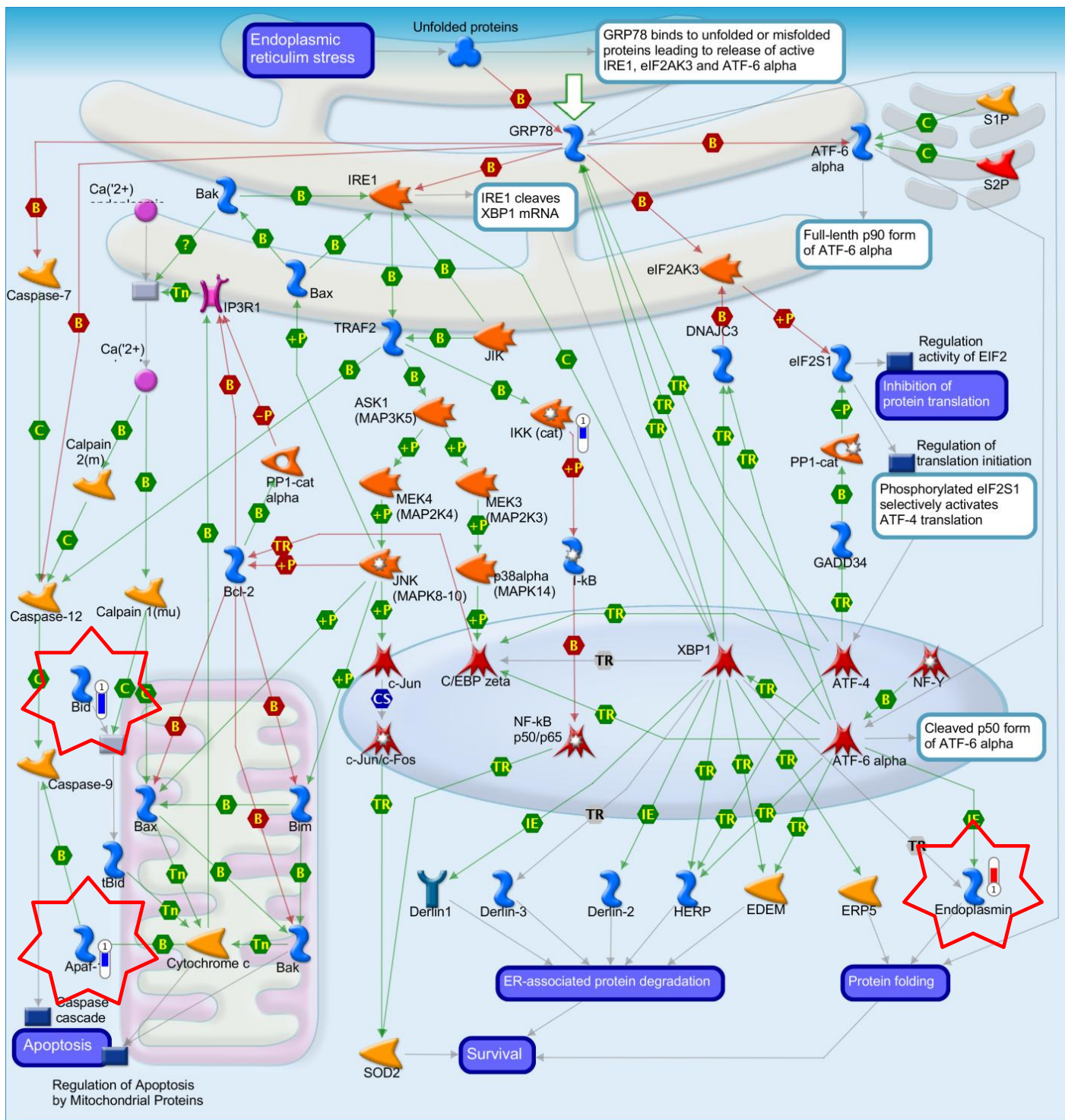
Figure S4



Higher expression in UM-CLL  
 Lower expression in UM-CLL

Enzymes  
 Protein kinase  
 Protein phosphatase

Receptor  
 Ligand  
 Binding proteins



Higher expression in UM-CLL  
 Lower expression in UM-CLL

Enzymes  
 Transcription factor  
 Binding proteins  
 Protein kinase  
 Generic protease